Concluding remarks

The challenge for the 21st century is to ensure toxicologists more effectively oppose poor science, inadequate interpretation of data, regulatory decisions that defy common sense and the misunderstanding over the use of experimental animals in toxicity testing. It is far easier for the uninformed to misinterpret data than it is for the expert to explain it in the context of actual risk. If we do not address these challenges, in another 100 years someone will be writing about the challenge facing toxicologists in the next century, still marvelling at our failure to tackle those of the past.

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Hormesis: U-shaped dose responses and their centrality in toxicology

Edward J. Calabrese and Linda A. Baldwin

The fundamental nature of the dose response is neither linear or threshold, but rather U-shaped. When studies are properly designed to evaluate biological activity below the traditional toxicological threshold, low-dose stimulatory responses are observed with high frequency and display specific quantitative features. With a few exceptions, the low-dose stimulatory response is usually not more than twofold greater than the control response, with a stimulatory zone that is more variable, ranging from less than tenfold to more than several orders of magnitude of the dose. Considerable mechanistic evidence indicates that hormetic effects represent overcompensations in response to disruptions in homeostasis that are mediated by agonist concentration gradients with different affinities for stimulatory and inhibitory regulatory pathways.

The field of toxicology is inherently centered on the design and conduct of experiments that characterize dose–response relationships and mechanisms that account for such responses. The nature of the dose response is therefore an essential feature of toxicology and is represented in detail in most toxicological texts. Several generations of toxicologists have been taught that the dose response is fundamentally sigmoidal but with a threshold operating at low doses. This conclusionary perspective dominated toxicological thinking up to the early 1970s, at which time cancer concerns increased; cancer causation was seen as stochastic phenomena with low-dose linearity becoming widely accepted and incorporated into risk-assessment practices by dominant US regulatory agencies [e.g. US Environmental Protection Agency (EPA) and US Food and Drug Administration (FDA)][1]. In fact, a dose–response dichotomy developed within the US EPA regulatory framework in which non-carcinogen responses were assumed to display a threshold whereas cancer responses were assumed to act via non-threshold (i.e. linear at low doses) means. Although there has been much controversy over the nature of the dose response (i.e. is it threshold or linear?), a re-invigorated hypothesis has emerged that the most fundamental shape of the dose response is neither linear nor threshold but, in fact, U-shaped. The U-shaped dose–response hypothesis has been referred to using numerous terms over the past century, including the Arndt–Schulz Law, Hueppe's Rule, the Yerkes–Dodson Law, hormesis, ecological subsidy, the theory of sufficient challenge, and others, depending on the biological sub-field of interest[2–6]. Regardless of the different terms used and the various biological fields, the descriptive features of the dose–response curves are remarkably similar.

Despite its lack of inclusion in leading modern textbooks of toxicology until recently[7], U-shaped dose

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responses have had a long and extensive history in the fields of chemical toxicology, radiation biology, microbiology, plant physiology and pharmacology[2–6]. In fact, so regular was the induction of U-shaped dose responses in experimental settings that such responses became incorporated as standard laboratory exercises and reliable information in university microbiological texts from the 1920s through the 1940s (Refs 8–11) were incorporated as components of national certification examinations[12] and were the subject of several journals dealing with experimental findings[13,14]. In addition, the scientific leaders who reported such findings during the formative stages of the field were recognized as being outstanding leaders and included: the internationally recognized bacteriologist Ferdinand Hueppe from Robert Koch's laboratory; the eclectic French scientist Charles Richet who later won the Nobel Prize for research on anaphylaxis; Gino Failla, a major national leader in the US concerned with radiation health issues, who obtained his PhD under Marie Curie; Louis Kahlenberg, Professor of Chemistry at the University of Wisconsin, who obtained his PhD under the Nobel laureate W. Ostwald at the University of Leipzig and initiated investigation into the biology of highly dilute solutions; Charles E.A. Winslow and his cadre of PhD students at Yale University in the 1920s and 1930s, who assessed the responses of bacteria to the salts of toxic metals; and numerous other scientific leaders of similar status[2–6].

'...a strong case can be made for the use of hormesis as a default assumption in the risk-assessment process.'

Nonetheless, the area of low-dose stimulation fell out of vogue by the late 1930s in both chemical toxicology and radiation biology as a result of a complex mix of factors. For example, hormetic responses are difficult to establish unequivocally because responses are modest being only 30–60% greater at maximum than control values. This results in heightened demands on study design features, including the number and spacing of doses, sample size, end-points selected and whether repeat measures were included. The modest response, the additional expense of larger sample sizes, additional doses and greater manpower needs, together with the additional emphasis and need for replication of findings given the modest response and the tendency of journals to publish more unequivocal findings combined to discourage research in this area[15]. Furthermore, the derivation of occupational exposure limits in the early to mid decades of the 20th century emphasized high-dose effects and the establishment of NOAELs and LOAELs (no observed adverse effect levels and lowest observed adverse effect levels) rather than sub NOAEL responses. Likewise, the water works industry, since the turn of the 20th century, has understandably emphasized the killing action of disinfectants rather than their recognized capacity to enhance bacterial colony growth at low doses[8–12]. In addition, various exaggerated claims for low-dose stimulation, which could not be sustained, had been made in the chemical and radiation fields for responses such as crop production and health enhancement. The net result was that experimentation emphasized the clarification of the biological effects of higher doses such as that needed to better define acute toxicities as well as chronic LOAELs and NOAELs whereas the U-shaped phenomenon at lower doses was not incorporated into the mainstream of toxicological testing, evaluation, regulation and education.

Despite its 'institutional' marginalization, U-shaped dose responses continued to be reported in the peer-reviewed literature in a broad range of biological disciplines. However, given limitations on study design, statistical power and reproducibility, findings supportive of hormetic effects often became more curiosity-like without sufficient staying power to generate long-term and broad-based scientific interest. This negative evaluation of hormetic responses has also been re-enforced by long-standing, ideological and scientific disputes between traditional medicine and homeopathy, the latter adopting the Arndt–Schulz Law as an explanatory principle of its medical practice. Further undercutting the concept of hormesis in the scientific community was the fact that not even its advocates could decide on what it was: a direct stimulatory response, a response that occurred only as an overcompensation to initial injury or a more complex concept that could incorporate both perspectives.

Given this turmoil, it is not unexpected that the concept of hormesis limped through the 20th century as a generally out-of-favor hypothesis with a few modest peaks of interest. However, just as the explosion of the atomic bomb brought renewed interest in the 20-year-old work of Muller[16] on radiation-induced mutation in *Drosophila*, which led to Muller being awarded the Nobel Prize in 1946, the enormous focus on low-dose linearity as the overwhelming driving force for cancer risk assessment and the numerous and costly environmental clean-ups led to a renewed interest in not only whether linearity was correct but whether it could even be proven incorrect! Thus, the external influence of the enormous cost of environmental clean ups and the proper allocation of limited societal resources have strongly encouraged a fresh and more sustained re-examination of evidence concerning hormesis, because if the hormesis hypothesis was viable the low-dose linearity paradigm might be strongly challenged on scientific grounds.

What is hormesis?

Hormesis is a dose–response phenomenon characterized by either a U-shaped or an inverted U-shaped dose response depending on the end-point

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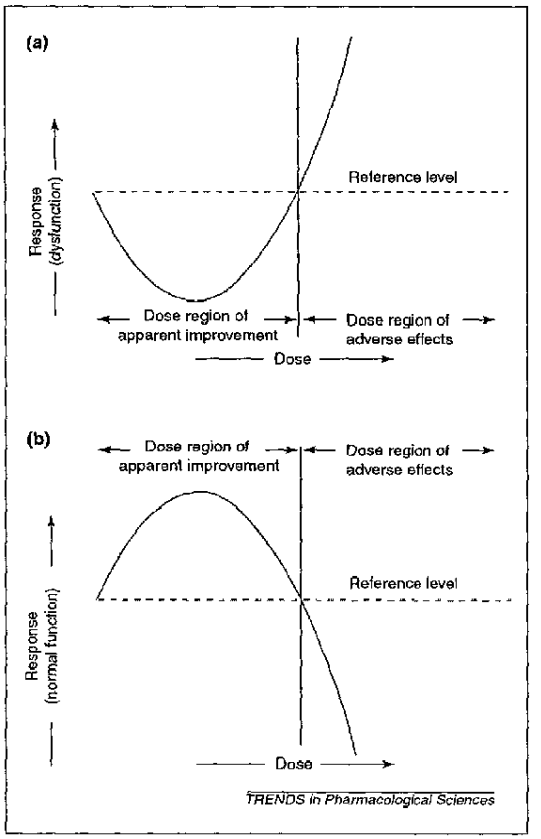

Fig. 1. U-shaped dose–response curves illustrating apparent (a) *reduced dysfunction* and (b) enhanced function[17].

measured[17] (Fig. 1). For example, the dose response would be U-shaped if the end-point were tumor incidence whereas the inverted U-shape could occur if longevity or growth had been measured. Hormesis characterizes the dose–response continuum as stimulatory at low doses and inhibitory at high doses, leading to the biphasic, hormetic dose–response curve.

Since the late 1890s it has been recognized that U-shaped dose–response curves might occur as a response to a disruption in homeostasis[18]. That is, at low levels of disruption or toxicity many biological systems display an overcompensation (other common terms in the literature are overshoot and rebound) response, which results in the apparent low-dose stimulation component of the response curve. At higher doses with greater initial toxicity, the system often displays a more limited capacity for a compensatory response, usually insufficient to return to control values. This process would lead to hormetic-like biphasic dose–response relationships. Numerous examples exist documenting that hormetic-appearing dose responses can represent a modest overcompensation to a disruption in homeostasis[19] (Fig. 2). This explanation can account for important and central features of the dose–response curve. That is, this explanation accounts for the continuous dose relationship of the low-dose stimulatory response to the traditional

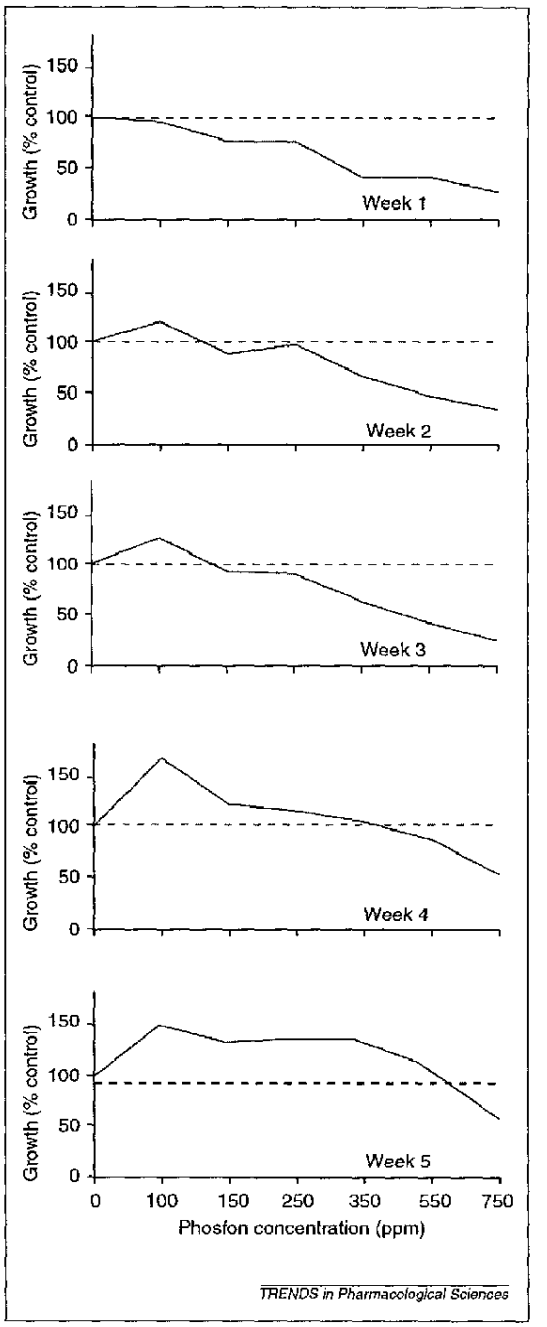

Fig. 2. Dose–response curves at various time points during an experiment with peppermint plants exposed to various concentrations of phosfon[15]. The graphs represent the overcompensation, rebound response following an initial dose-dependent decrease in growth. The rebound response might account for the low-dose stimulatory response referred to as hormesis. Reproduced, with permission, from Ref. 15. ©Society for Risk Analysis.

toxicological NOAEL, for the limited stimulatory range (usually 10–20-fold below the NOAEL) and the modest stimulatory response (usually 30–60% maximum). The linkage of hormetic responses to

Box 1. Representative receptor systems displaying biphasic dose–response relationships[a]

Adenosine	Neuropeptides
Adrenoceptor	Nitric oxide
Bradykinin	*N*-methyl-D-aspartate
Cholecystokinin	Opioid
Corticosterone	Platelet-derived growth factor
Dopamine	Prolactin
Endothelin	Prostaglandin
Epidermal growth factor	Somatostatin
Estrogen	Spermine
5-HT	Testosterone
Human chorionic gonadotropin	Transforming growth factor β
Muscarinic acetylcholine	Tumor necrosis factor α

Reference

a Calabrese, E.J. and Baldwin, L.A., eds Scientific foundations of hormesis. *Crit. Rev. Toxicol.* (in press)

homeostasis provides a crucial evolutionary foundation to account for this adaptive response within the context of a physiologically based biological feedback system of an optimized expenditure of resources. Linked in this way to an evolutionarily based control system that is designed to restore homeostasis, only modest overcompensation (i.e. limited stimulatory responses) would be predicted. Despite this recognition that hormetic responses can occur as a result of modest overcompensation to a disruption in homeostasis, most hormetic dose–responses lack adequate temporal data to address this issue. In addition, an array of studies exists displaying the hormetic-like biphasic dose response that appears to result from a direct stimulation at low doses and inhibition at higher doses without involvement of the abovementioned compensatory responses. These observations underscore the phenomenological nature of the hormesis concept and the suggestion of mechanistic complexity.

Molecular mechanisms to account for hormetic-like biphasic dose responses are numerous, being most thoroughly documented in the pharmacological literature with respect to receptor-based systems. In an assessment of several dozen pharmacologically based receptor systems (Box 1) that affect a broad range of crucial physiological and behavioral responses, essentially all display biphasic responses[19]. In many instances, pharmacological systems have evolved highly efficient biological regulatory strategies in which the same endogenous agonist can elicit a stimulatory or inhibitory response depending on its concentration. Multiple examples exist that link pollutant-enhanced changes in endogenous agonist concentrations with biphasic dose responses[19]. The linking of molecular pharmacological mechanisms with hormetic-like toxicological responses represents an important step in providing a general mechanistic understanding of the plethora of descriptive findings of a hormetic nature in the toxicological literature.

Occurrence of hormesis in toxicological literature

Two types of databases have been developed to assess hormesis. One is focused on: (1) the occurrence of hormetic responses and their quantitative evaluation for consistency with the biphasic β-dose–response curve; (2) information on study design, dose–response and statistical features; (3) reproducibility of findings; and (4) availability of underlying mechanisms, among other relevant features[20,21]. The second database employed rigorous *a priori* entry and evaluative criteria to assess the proportion of dose responses in the toxicological literature that displays hormetic responses[22]. An assessment of over 20 000 articles from three environmentally and pharmacologically oriented toxicology journals revealed that ~668 dose responses satisfied the entry criteria with 37% of the 668 dose responses satisfying the evaluative criteria. A further assessment of individual treatment doses below the NOAEL, rather than dose responses, indicated that hormetic-like statistically significant stimulatory responses occurred more frequently by ~15-fold than a statistically significant negative response, thereby providing strong support for the position that below NOAEL, low-dose stimulatory responses cannot be explained by random variation.

The findings in the hormetic databases are not restricted by end-point, biological model and chemical class or physical agent. The high frequency of hormetic responses in the toxicological literature and this lack of restriction into the principal extrapolative areas of concern argues strongly for their broad-based occurrence in biological, pharmacological, toxicological and public health domains.

Observing and evaluating hormesis

Given its marginalized history and dose–response characteristics that place heightened demands on study design features, it is not unexpected that examples of hormesis are not easily observed, even with sophisticated databases. Thus, the search for hormetic responses even in the toxicological literature reveals that 98–99% of studies cannot even address the hypothesis in an adequate manner. This can create the impression that hormesis is a rare and paradoxical phenomenon when, in fact, it is not if study design requirements are adhered to. The developing hormesis relational and retrieval databases described above were designed, in part, to provide an efficient means to access articles subjected to *a priori*, objective criteria concerning consistency with the hormetic hypothesis. These databases, described in previous publications[15,20–22], include numerous study design features and response parameters. In addition to these developing databases, substantial information that summarizes hormetic effects on their capacity for generalization,

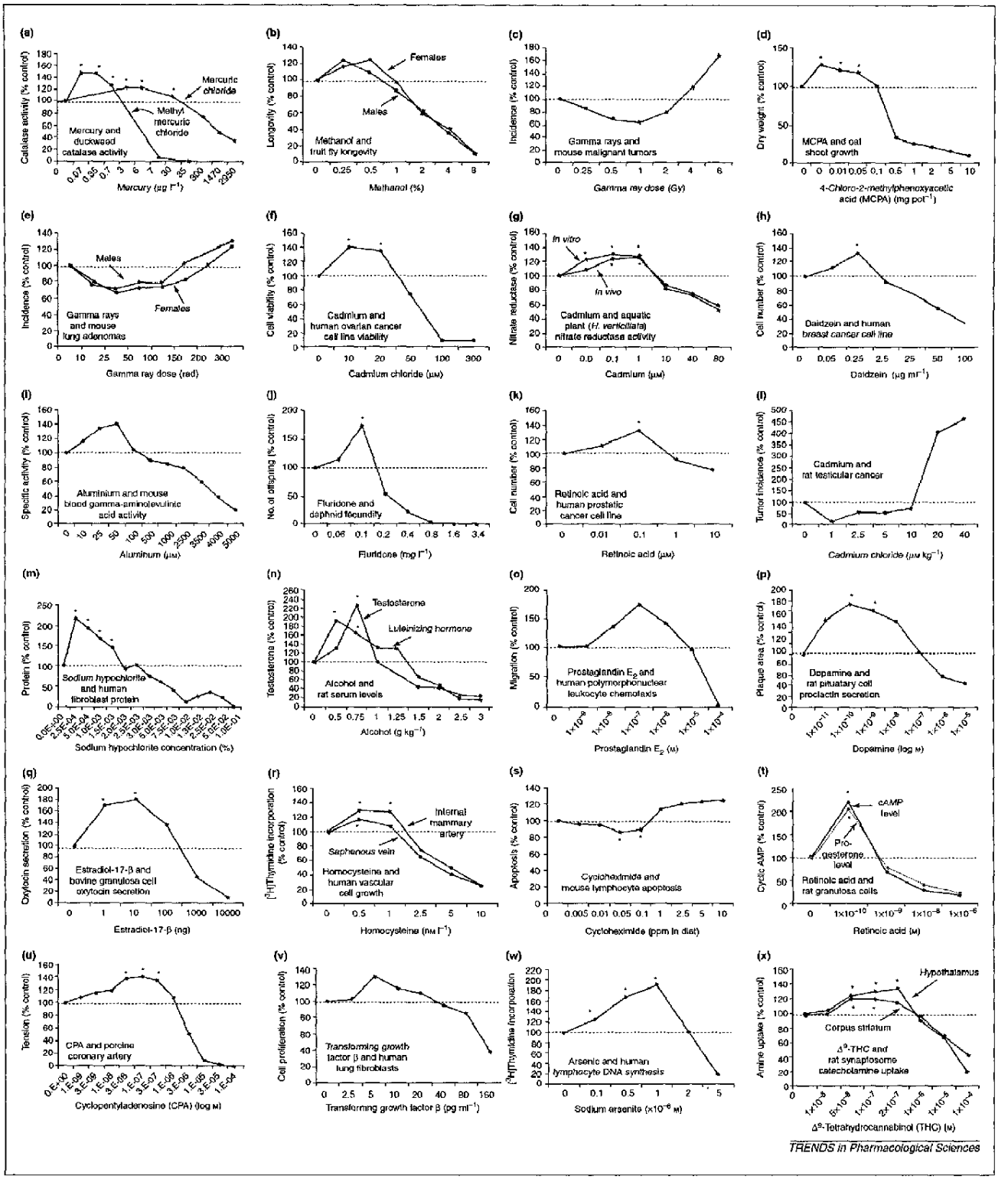

Fig. 3. Representative examples of U-shaped dose–response curves. The asterisks indicate statistically significant data; absence of statistical significance denotes studies that did not perform statistical analyses on their data with the exception of (l), in which the lowest four responses were not statistically significantly different from the control. Sources of data for (a–x) are Refs 31–54, respectively.

overcompensation responses and pharmacological mechanisms has been reported recently[19]. Nonetheless, Fig. 3 provides several examples of responses that are consistent with the hormetic hypothesis. These examples were selected principally to illustrate the range of biological models and end-points in which hormetic responses might occur.

Implications of hormesis

The issue of the biological effects of low-level exposures to chemical and/or physical agents is a principal focus for toxicological assessment. Emphasis on high-dose exposures is progressively yielding to the need to reflect actual exposures of workers and the general public, which are often precipitously lower than those several decades ago. Such recognition of lower exposures would not be expected to be a major concern if traditional linear extrapolation procedures were reliable and if NOAELs with threshold responses were established in hazard assessment. However, the hormetic phenomenon indicates that statistically and biologically significant responses frequently occur below the NOAEL, thereby revealing both the limitations and inadequacy of past and current low-dose extrapolation procedures. These findings have important implications for the hazard assessment process, study design, animal model selection and the risk-assessment process used by environmental and public health regulatory agencies. Given the frequency and broad-based general applicability of hormetic responses in the toxicological literature a strong case can be made for the use of hormesis as a default assumption in the risk-assessment process. If hormesis had to be 'proven' for each chemical and within each experiment, it would be necessary to drastically change how hazard assessment is performed, starting with animal model selection. For example, most chronic bioassays use models with low background disease incidence for very practical resource and statistical reasons. Yet, the use of models with low background incidence precludes an assessment of hormesis because the U-shaped curve could not be assessed. Thus, it is impossible even to test the hormesis hypothesis in many commonly employed experimental model systems for end-points of public health concern. The question of how much supporting evidence is needed to transform hormesis from a widespread phenomenon to an accepted default assumption in the risk-assessment process is a central implication.

Hormetic-like biphasic dose responses also have important implications in the area of chemo- and radiotherapeutics. Low-dose stimulation of the immune system by whole body radiation has been shown to prevent metastases and tumor incidence in animal models injected with cells from well known tumor cell lines. Preliminary clinical follow-up investigations based on these findings suggest that similar reductions in human cancer incidence might also occur[23–25].

The hormetic-like biphasic response is also observed in other biological disciplines although it is referred to using different terms. For example, the field of experimental psychology uses the phrase Yerkes–Dodson Law to represent the biphasic nature of the relationship of the magnitude of stress and the learning response curve under different complexities of assigned tasks. The implications of such biphasic stress-related responses are widespread. For example, high levels of stress by eyewitness observers of a violent crime often result in poor memory of specific events. Follow-up research has linked such findings to the release of high quantities of glucocorticoids whereas at lower doses they enhance memory[26–28].

Retinoic acid can suppress the development of various epithelial tumors whereas at lower doses it can affect cell proliferation (i.e. tumor promotion). Such biphasic responses are observed frequently with antibiotics, antiviral agents, non-steroidal anti-inflammatory drugs (NSAIDS) and numerous other agents[29,30].

The future of toxicology and pharmacology will have to come to terms with the emerging reality that toxicological dose–response relationships are more complex than previously recognized and that traditional evaluative extrapolation procedures are often no longer viewed as providing accurate estimates of response at low doses. Although the concept of hormesis, therefore, is likely to profoundly impact the risk-assessment process, including features of hazard assessment such as study design, statistical power considerations, model and end-point selection, and risk modeling approaches, it will also create opportunities to enhance public decisions on resource allocations for risk-based questions and for ensuring that chemo- and radio-therapeutic treatments achieve optimized goals. Thus, with low doses as a present and future reality, recognition of hormetic effects will assist in their proper assessment and utility. To continue to ignore this reality is one that society can do only at its own financial and health risk.

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